C2 concld.

b) contacting said immortalized cell with a composition comprising at least one HIV virus; and,

c) assaying for marker gene expression to thereby detect the HIV virus.

C3

48. (Amended) The method of claim 43, wherein said marker gene encodes luciferase, β-galactosidase, green fluorescent protein, or a polypeptide that confers antibiotic resistance.

REMARKS

Status of the Claims

Claims 37-86 are pending in the present application. Claims 39, 43, and 48 have been amended as suggested by the Examiner. Reexamination and reconsideration of the claims are respectfully requested. The Examiner's remarks in the Office Action are addressed below in the order set forth in the Office Action.

The Objections to the Claims Should be Withdrawn

The Examiner objected to claims 39 and 48 on the grounds that these claims should recite a polypeptide that confers antibiotic resistance. Claims 39 and 48 have been amended as suggested by the Examiner, thereby obviating the objection.

The Rejections of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claim 38 was rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is indefinite for reciting that the "cell originates from HeLa." Claims 38 has been amended to recite that the cell originates from a HeLa cell. It is respectfully submitted that the rejection should not be applied to the amended claim for the reasons described below.

Claim 38 as amended recites the immortalized cell line of claim 37, wherein the cell originates from a HeLa cell. The specification of the present application describes the

modification of a HeLa cell to produce a cell that meets the limitations of claim 37, *i.e.* an immortalized cell characterized as expressing CCR5, CXCR4, and CD4 receptors and having stably incorporated a marker gene operably linked to a promoter where expression of the marker gene occurs upon HIV infection of the cell. *See,* pages 7-9 and pages 13-16 of the specification. One of ordinary skill in the pertinent art, reading claim 38 in light of the support in the specification would recognize that a cell that originates from a HeLa cell as recited in the claim is a HeLa cell that has been modified such that it has one or more characteristic that is different from that of the parent HeLa cell. Accordingly, one of ordinary skill in the pertinent art would be able to ascertain with reasonable precision and particularity the particular area set out and circumscribed by this claim.

Claim 41 was rejected under 35 U.S.C. § 112, second paragraph, on the grounds that it is indefinite for reciting that the cell is sensitive to HIV infection "to a degree similar to" a primary blood mononuclear cell. The rejection is respectfully traversed for the reasons described below.

The Federal Circuit has stated that if the claims, read in light of the specification, reasonably apprise those skilled in the art of the use and scope of the invention, and if the language is as precise as the subject matter permits, the claims are definite under 35 U.S.C. § 112, second paragraph. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 USPQ 634 (Fed. Cir.), *cert. dismissed*, 474 U.S. 976 (1985). Claim 41 meets this standard. This claim recites an immortalized cell of claim 37 wherein the cell is sensitive to HIV infection to a degree similar to a primary peripheral blood mononuclear cell. Table 1, found on page 24 of the specification and Table 2, found on page 25 of the specification, show HIV sensitivity for a line of cells meeting the limitations of claim 37 (J53-C16) and for a primary peripheral blood mononuclear cell line (PBMC). These tables demonstrate that the sensitivity to HIV infection for the J53-C16 and PBMC cell lines varies depending on the HIV isolate used. However, the sensitivities of the two cell lines were similar for each HIV isolate tested, with the values for infectivity falling within approximately two to twenty-one fold of each other. *See*, pages 24-25 of the specification. Accordingly, the phrase "wherein said cell is sensitive to HIV infection to a

degree similar to a primary blood mononuclear cell," when read in light of the specification, apprises those of skill in the art of the scope of the claim. Furthermore, this language is as precise as the subject matter permits, because sensitivity to HIV infection varies according to the HIV strain tested. Therefore, the language of claim 41 meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 43 was rejected under 35 U.S.C. § 112, second paragraph, because it does not recite a correlative step in the method that unites the conclusion of the method with the preamble of the claim. Clause (c) of claim 43 has been amended to recite the step of assaying for marker gene expression to thereby detect the HIV virus. This amendment obviates the rejection.

Claim 43 has further been rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the purpose of the method is unclear. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that while the method of claim 43 is directed to detecting an HIV virus, clause (b) of this claim recites that the composition with which the cell line is contacted comprises at least one HIV virus, and therefore detection of the virus would not be required. Applicants note that claim 43 does not recite that the composition ***must be known*** to comprise at least one HIV virus prior to performing the method. Rather, the claimed method will detect an HIV virus only in compositions that contain such a virus. If a composition does not contain an HIV virus, then no HIV virus can be detected using the method. Accordingly, one of ordinary skill in the pertinent art would be able to ascertain with reasonable precision and particularity the particular area set out and circumscribed by this claim.

Claim 45 was rejected under 35 U.S.C. § 112, second paragraph on the grounds that it is indefinite. The rejection is respectfully traversed for the reasons described below.

Claim 45 recites the method of claim 43, further comprising the step of isolating the HIV virus. The Examiner argues that if the composition recited in claim 43 is known to contain HIV, the virus is already isolated in the sample. However, claim 43 does not recite that the

composition is known to contain an HIV virus as described above. Accordingly, the scope of the claim would be clear to one of skill in the pertinent art.

Claims 46 and 49 was rejected under 35 U.S.C. § 112, second paragraph, on the grounds that they are indefinite. The rejection is respectfully traversed for the reasons described below.

The Examiner states that claims 46 and 49 are indefinite because they recite a "primary HIV virus." As an initial matter, Applicants note that claim 49 does not recite a "primary HIV virus;" therefore, it is assumed that the rejection is intended to be applied to claims 46 and 47. Furthermore, the term "primary HIV" is defined on lines 1-3 of page 7 of the specification. The Examiner notes that a definition of this phrase is provided in the specification but argues that the meaning of the phrase "remains unclear." August 12, 2002 Office Action, page 4.

The Board of Patent Appeals and Interferences has stated that:

> In rejecting a claim under the second paragraph of 35 USC 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims.

Ex parte Wu, 10 USPQ2d 2031, 2033 (B.P.A.I. 1989). In the present case, no evidence or reasoning has been provided to demonstrate that definition of the phrase "primary HIV" found in the specification would not allow one of ordinary skill in the pertinent art to determine the particular area set out by the claims. In fact, the definition provided in the specification, which states that "primary HIV" is defined as HIV derived directly from an infected host organism from sources such as blood, plasma, PBMC, CSF, and other tissues, is sufficient to allow one of skill in the pertinent art to ascertain the metes and bounds of the claims. In rejecting claims 46 and 47 for indefiniteness, the Examiner asks what a secondary virus would be; however the phrase "secondary HIV" is not recited in any of the claims, or in the specification and it is unclear to the Applicants, in the absence of further explanation, why this inquiry is relevant to the definiteness of claims 46 and 47.

In view of the above arguments and amendments, all grounds for rejection under 35 U.S.C. § 112, second paragraph, have been overcome. Reconsideration and withdrawal of the rejections are respectfully requested.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 43-49 were rejected under 35 U.S.C. §112, first paragraph, on the grounds that the specification does not provided enablement for the claimed methods. This rejection is respectfully traversed for the reasons described below.

Claims 43-49 are drawn to methods for detecting HIV virus. The method recited in claim 43 as amended comprises the steps of: a) providing an immortalized cell characterized by expressing CCR5, CXCR4, and CD4 receptors and having stably incorporated a marker gene operably linked to a promoter, wherein expression of the marker gene occurs upon HIV infection of the immortalized cell; b) contacting said immortalized cell with a composition comprising at least one HIV virus; and, c) assaying for marker gene expression to thereby detect the HIV virus.

The Examiner argues that while the specification provides sufficient enablement for detecting viral particles, the specification does not provide enablement for detecting one HIV virus. As an initial matter, Applicants note that the method of claim 43 is directed to methods of detecting an HIV virus in a composition comprising ***at least one*** HIV virus. Accordingly, the claim is not limited to embodiments in which the composition contains only one HIV virus. Furthermore, there is no requirement that every embodiment within the scope of the claim be operative in order to satisfy the enablement requirement. The Federal Circuit has indicated that a claim is not necessarily invalid because it includes inoperative embodiments, and that "[i]t is not a function of the claims to specifically exclude possibly inoperative substances." *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984). In the present case, Applicants have demonstrated that a cell line meeting the limitations of clause (a) of claim 43 can be used to detect extremely low numbers of HIV infectious units. *See*, Figure 5 and Example 2 on pages 14-16 of the specification. Accordingly, the vast majority of embodiments

falling within the scope of the claims are operative, and one of ordinary skill in the art would not have to experiment unduly in order to practice the claimed invention.

The Examiner cites Splenlehauer *et al.* (2001) *Virology 280*:292-300 in support of the assertion that one skilled in the art would not be able to detect one HIV virus in a sample due to the detection limits of reporter systems. The Examiner refers to Figure 2 of this reference and infers from this figure that "a viral titer of at least 0.03 to 0.12 $TCID_{50}$ is required to produce reporter activity, depending on viral subtype." August 12, 2002 Office Action, page 4. However, this is not the conclusion drawn by the authors of the Spenlehauer *et al.* reference. In fact, the authors do not draw any conclusions regarding the lower limit for detection of HIV virus using a reporter gene system. Furthermore, the specification of the present application provides ***working examples*** that demonstrate that very low levels of HIV virus can be detected using the claimed method. *See*, for example, Figure 5 and Example 3. Accordingly, the Splenlehauer *et al.* reference does not support the argument that undue experimentation would be required to practice the method of claim 43.

The Examiner argues that the method of claim 44 is not enabled because "the skilled artisan would doubt that the instant cell line would be accurate for determining viral titers." August 12, 2002 Office Action, page 4. However, the specification provides ***working examples*** demonstrating that cells meeting the limitations of clause (a) of claim 43 can be successfully used to obtain a sensitive and accurate viral titer. *See*, Figures 5, 6, and 7 and Examples 2 and 3 on pages 13-18 of the specification. Furthermore, the specification demonstrates that the HIV sensitivity of the J53-C13 cell line, which meets the limitations of clause (a) of claim 43, is similar to that of primary bone marrow cells (PBMC). As noted by Spenlehauer *et al.* (cited by the Examiner), PBMC are the most commonly used target cells for assaying HIV viral titer. The skilled artisan would not doubt that the cell recited in claim 43 could be used to quantitate the level of infectious HIV units as recited in claim 44 because the specification provides direct experimental evidence demonstrating that a cell meeting the limitations of claim 43 can be used in the method of claim 44.

The Examiner cites Roos *et al.* (2000) *Virology 273*:307-305 in support of the assertion that one of skill in the art would doubt that the cell line recited in claim 43 could be used to accurately determine viral titers. Roos *et al.* state that the MAGI and sMAGI cell lines are not representative of HIV/SIV host cells *in vivo*. However, the present invention is not directed to the use of the MAGI and sMAGI cell lines for detecting HIV. These cell lines do not meet the limitations set forth in clause (a) of claim 43. Furthermore, the specification of the present application presents direct experimental evidence that a cell meeting the limitations of claim 43 can be used in the method of claim 44 to quantitate the level of infectious HIV units.

The Examiner states that Roos *et al.* teach that the antiviral drug AZT has limiting quantitative influences on β-gal expression. Contrary to the suggestion made by the Examiner, Roos *et al.* do not teach that AZT interacts directly with the expression products of reporter genes to reduce their detection. Rather, Roos *et al.* teach that AZT decreases SIV-induced reporter gene expression because it blocks replication of the virus and therefore decreases the number of infectious HIV virions. In the experiment referred to by the Examiner, Roos *et al.* used AZT as a chemical tool to allow detection of a single SIV replication cycle. *See*, Roos *et al.*, page 309, column 2. In this experiment, the authors infected LuSIV cells with SIV, washed off the virus inoculum, and then treated the cells with AZT for the remainder of the infection. Roos *et al.* state that "since AZT inhibits RT activity, the luciferase activity detected 24 hr post infection reflects the infectivity of those virions that entered and initiated reverse transcription prior to AZT treatment." Roos *et al.*, page 309, column 2.

Based on the experiment described by Roos *et al.*, the Examiner infers that "if a sample derived from a patient taking AZT is contacted with the instant cell line, reporter gene sensitivity will diminish." To the extent that a patient being treated with AZT will have a lower viral titer, this statement is true. However, the lower titer viral titer will result from an actual decrease in the number of HIV virions, not from an interaction between AZT and the reporter gene expression product. Furthermore, it is has long been recognized that resistant viral strains of HIV develop in patients reciting AZT treatment. Thus, even in samples from a patient undergoing therapy with AZT, viral particles that have not yet been inhibited by AZT and viral particles that

have become resistant to AZT will be present in many cases and will therefore be detected by the methods present invention.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 112, first paragraph have been overcome. Reconsideration and withdrawal of the rejections are therefore respectfully requested.

The Rejection under 35 U.S.C. § 103 Should be Withdrawn

Claims 37-49 and 65 have been rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over U.S. Patent No. 6,258,426 and Chackerian *et al.* (1997) *J. Virol.* 71:3932-39. The rejection is respectfully traversed for the reasons described below.

U.S. Patent No. 6,258,246 teaches a cell line that expresses CD4, CCR5, and a reporter gene, and a cell line that expresses CD4, CXCR4, and a reporter gene. This patent does not teach a cell line expressing CD4, CRR5, and CXCR4, and does not suggest that it would be advantageous to express all three receptors together in a cell line with a reporter gene, or to use such a cell line for detecting HIV.

Chackerian *et al.* teaches a cell line that expresses CD4, CCR5, and CXCR4. This reference does not teach or suggest a cell line expressing the CD4, CCR5, and CXCR4 receptors where the cell line contains a marker gene operably linked to a promoter and expression of the marker gene occurs upon HIV infection of the cell. This reference also does not teach the use of such a cell line in a method for detecting HIV.

The Examiner argues that it would be obvious to one of ordinary skill in the art to combine the teachings of U.S. Patent No. 6,258,427 and Chackerian *et al.* to produce a cell line meeting the limitations of claim 37. In *In re Vaeck,* 20 USPQ2d 1438 (Fed. Cir. 1991), the Federal Circuit held that:

> Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, a proper analysis requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed compositions or device, or carry out the claimed process; and (2) whether the prior art would

> also have revealed that in so making and carrying out, those of ordinary skill would have a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Vaeck at 1442, *citing In re Dow Chemical Co.*, 5 USPQ2d 1459, 1531 (Fed. Cir. 1988). Furthermore, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *Manual of Patent Examining Procedure* § 2143.01 (8th ed.), citing *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990).

In the present case, no *prima facie* case of obviousness has been established because there is no suggestion in the prior art to combine the cited references. The cited references do not suggest the desirability of a cell expressing CCR5, CXCR4, and CD4, where the cell has stably incorporated a marker gene operably linked to a promoter, where the expression of the marker gene occurs upon HIV infection of the cell. Thus, the cited references provide no motivating suggestion to create a cell line meeting all of the limitations of claim 37. The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). In addition, the references must be viewed without the impermissible hindsight vision afforded by the claimed invention. *Manual of Patent Examining Procedure* § 2141, *citing Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 (Fed. Cir. 1986). In the present case, it is the Applicants' disclosure of the desirable properties of the cell line of claim 37, rather than the prior art, that provides the motivation to one of skill in the art to modify the disclosures of U.S. Patent No. 6,258,246 and Chackerian *et al.*

Furthermore, one of skill in the art would not have expected that a cell line meeting the limitations of claim 37 would have the desirable characteristics of the cell lines described in the instant application. The instant application teaches a cell line meeting the limitations of claim 37, and shows that this cell line is sensitive to HIV infection to a degree similar to peripheral blood mononuclear cells and can be used to detect low numbers of virus infectious units. *See*, Table 1 and page 16, lines 1-4 of the specification. The instant application also teaches that this

cell line gives a near-linear range of detection for HIV titers between 10 and 10,000 infectious units. *See*, Figures 5 and 6 and lines 9-19 on page 15 of the specification. Based on the teachings in the prior art, one of skill in the art would not have predicted that a cell expressing CCR5, CXCR4, and CD4, where the cell has stably incorporated a marker gene operably linked to a promoter, and where the expression of the marker gene occurs upon HIV infection of the cell would be have a near-linear range of detection for HIV over such a broad range of titers. Rather, it is the Applicants' disclosure that teaches the unexpected characteristics of a cell meeting the limitation of claim 37.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 103(a) have been overcome. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

It is believed that all the rejections have been obviated or overcome and the claims are in conditions for allowance. Early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject Application, the Examiner is invited to call the undersigned agent.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

Kathryn L. Coulter

Kathryn L. Coulter
Registration No. 45,889

Customer No. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Raleigh Office (919) 862-2200
Fax Raleigh Office (919) 862-2260

"Express Mail" Mailing Label Number EL868644442US
Date of Deposit: **January 13, 2003**
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Commissioner for Patents, Washington, DC 20231.

Nora C. Martinez

Version with Markings to Show Changes Made

In the Claims:

Please amend claims 39, 43, and 48 as follows.

39. (Amended) The immortalized cell of claim 37, wherein said marker gene encodes luciferase, β-galactosidase, green fluorescent protein, or a polypeptide that confers[infers] antibiotic resistance.

43. (Amended) A method for detecting a HIV virus comprising:

d) providing an immortalized cell characterized by expressing CCR5, CXCR4, and CD4 receptors and having stably incorporated a marker gene operably linked to a promoter, wherein expression of the marker gene occurs upon HIV infection of the immortalized cell;

e) contacting said immortalized cell with a composition comprising at least one HIV virus; and,

f) assaying for marker gene expression to thereby detect the HIV virus.

48. (Amended) The method of claim 43, wherein said marker gene encodes luciferase, β-galactosidase, green fluorescent protein, or a polypeptide that confers[infers] antibiotic resistance.